

CLAIMS:

1. An isolated nucleic acid sequence, of an alternative splicing variant of tumor necrosis factor receptor (TNFR), selected from the group consisting of:

(i) the nucleic acid sequence depicted in any one of SEQ ID NO: 1 to
5 SEQ ID NO: 8;

(ii) nucleic acid sequences having at least 90% identity with the sequence of (i); and -

(iii) fragments of (i) or (ii) of at least 20 b.p., provided that said fragment contains a sequence which is not present, as a continuous stretch of nucleotides, in
10 the original nucleic acid sequence of TNFR from which the sequences of (i) have been varied by alternative splicing.

2. An isolated nucleic acid sequence complementary to the nucleic acid sequence of Claim 1.

3. An amino acid sequence selected from the group consisting of:

(i) an amino acid sequence coded by the isolated nucleic acid sequence
15 of alternative splice variants of Claim 1;

(ii) homologues of the amino acid sequences of (i) in which one or more amino acids has been added, deleted, replaced or chemically modified in the region, or adjacent to the region, where the amino acid sequences differs from the original
20 amino acid sequence, coded by the original TNFR nucleic acid sequence from which the variant has been varied by alternative splicing.

4. An amino acid sequence according to Claim 3, as depicted in any one of SEQ ID NO:9 to SEQ ID NO:16.

5. An isolated nucleic acid sequence coding for any one of the amino acid
25 sequences of Claim 3 or 4.

6. A purified antibody which binds specifically to any of the amino acid sequence of Claim 3 or 4.

7. A purified antibody which binds to an amino acid sequence which is present only in the alternative splice variant depicted in the amino acid of Claims 3 or 4,
30 but is not present in the amino sequence of TNFR.

8. A purified antibody which binds to an amino acid sequence present in the amino acid sequence of TNFR which amino acid sequence is not present in the amino acid sequence of Claims 3 or 4.
9. An expression vector comprising any one of the nucleic acid sequences of
5 Claim 1 or 5 and control elements for the expression of the nucleic acid sequence in a suitable host.
10. An expression vector comprising any one of the nucleic acid sequences of Claim 2, and control elements for the expression of the nucleic acid sequences in a suitable host.
- 10 11. A host cell transfected by the expression vector of Claim 9 or 10.
12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active ingredient an agent selected from the group consisting of:
 - (i) the expression vector of Claim 9; and
 - (ii) any one of the amino acid sequences of Claim 3 or 4.
- 15 13. A pharmaceutical composition according to Claim 12, for treatment of diseases which can be ameliorated, cured or prevented by raising the level of any one of the amino acid sequences depicted in SEQ ID NO:9 to SEQ ID NO:16.
14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as an active ingredient an agent selected from the group consisting of:
 - 20 (i) any one of the nucleic acid sequences of Claim 2;
 - (ii) the expression vector of Claim 10; and
 - (iii) the purified antibody of Claim 6 or 7.
- 15 15. A pharmaceutical composition according to Claim 14, for treatment of diseases which can be ameliorated, cured or prevented by lowering the level of any
25 one of the amino acid sequences depicted in SEQ ID NO:9 to SEQ ID NO:16.
16. A method for detecting the presence of a variant nucleic acid sequence of TNFR in a biological sample, comprising the steps of:
 - (a) hybridizing to nucleic acid material of said biological sample any one
of the nucleic acid sequences of Claim 1 or 2; and
 - 30 (b) detecting said hybridization complex;

wherein the presence of said hybridization complex correlates with the presence of an variant nucleic acid sequence in the said biological sample.

17. A method for determining the level of variant nucleic acid sequences of TNFR in a biological sample comprising the steps of:

5 (a) hybridizing to nucleic acid material of said biological sample any one of the nucleic acid sequences of Claim 1 or 2; and

(b) determining the amount of hybridization complexes and normalizing said amount to provide the level of the variant nucleic acid sequences in the sample.

10 18. A method for determining the ratio between the level of the nucleic acid sequence of a TNFR variant in a first biological sample and the level of the original TNFR sequence from which the variant has been varied by alternative splicing, in a second biological sample comprising:

(a) determining the level of the TNFR variant nucleic acid sequence in
15 the first biological sample according to the method of Claim 17;

(b) determining the level of the TNFR original sequence in the second biological sample; and

(c) comprising the levels obtained in (a) and (b) to give said ratio.

19. A method according to Claim 18, wherein said first and said second
20 biological samples are the same sample.

20. A method according to any of Claims 16 to 19, wherein the nucleic acid material of said biological sample are mRNA transcripts.

21. A method according to Claim 20, where the nucleic acid sequence is present in a nucleic acid chip.

25 22. A method for identifying candidate compounds capable of binding to the variant product and modulating its activity the method comprising:

(i) providing any one of the amino acid sequences as defined in Claim 3 or 4;

(ii) contacting a candidate compound with said amino acid sequence;

(iii) determining the effect of said candidate compound on the biological activity of said protein or polypeptide and selecting those compounds which show a significant effect on said biological activity.

23. A method according to Claim 22, wherein the compound is an agonist and
5 the measured effect is increase in the biological activity.

24. A method according to Claim 22, wherein the compound is an antagonist and the effect is decrease in the biological activity.

25. An agonist of any one of the amino acid sequences of Claim 3 or 4.

26. An antagonist of any one of the amino acid sequences of Claims 3 or 4.

10 27. A method for detecting any one of the amino acid sequences of Claim 3 or 4 in a biological sample, comprising the steps of:

(a) contacting with said biological sample the antibody of Claim 6 or 7, thereby forming an antibody-antigen complex; and

(b) detecting said antibody-antigen complex

15 wherein the presence of said antibody-antigen complex correlates with the presence of the desired amino acid in said biological sample.

28. A method for detecting the level of the amino acid sequence of any one of Claim 3 or 4 in a biological sample, comprising the steps of:

(a) contacting with said biological sample the antibody of Claim 6 or 7,
20 thereby forming an antibody-antigen complex; and

(b) detecting the amount of said antibody-antigen complex and normalizing said amount to provide the level of said amino acid sequence in the sample.

29. A method for determining the ratio between the level of any one of the
25 amino acid sequences of Claims 3 or 4 of variant TNFR present in a first biological sample and the level of the original TNFR amino acid sequences from which they were varied by alternative splicing, present in a second biological sample, the method comprising:

(a) determining the level of the amino acid sequences of Claims 3 or 4
30 into a first sample by the method of Claim 28;

(b) determining the level of the original TNFR amino acid sequence in the second sample; and

(d) comparing the level obtained in (a) and (b) to give said ratio.

30. A method according to Claim 29, wherein said first and said second
5 biological samples are the same sample.